

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE
COMPANY, JOHN HANCOCK
VARIABLE LIFE INSURANCE
COMPANY and MANULIFE
INSURANCE COMPANY,

Plaintiffs,

v.

ABBOTT LABORATORIES,

Defendant.

CIVIL ACTION NO. 05-11150-DPW

**ABBOTT'S CORRECTED DEPOSITION COUNTER DESIGNATIONS FOR
BRUCE RODDA**

Defendant Abbott Laboratories (“Abbott”) respectfully submits the attached corrected deposition counter-designations for the June 6, 2007 deposition of Bruce Rodda, Ph.D., Clinical Trials and Statistics Expert.

Dated: February 21, 2008

Respectfully submitted,

ABBOTT LABORATORIES

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CERTIFICATE OF SERVICE

I hereby certify that this document(s) filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies will be sent to those indicated as non registered participants on February 21, 2008.

Date: February 21, 2008.

/s/ Ozge Guzelsu

Bruce Rodda Deposition Designations

Depo Date	Witness	Hancock Designation	Abbott Counter Designation	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
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Depo Date	Witness	Hancock Designation	Abbott Counter Designation	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
6/6/2007	Rodda, Bruce		93:1-93:17				
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Color Key to Deposition Designations

Designation by Plaintiffs

Counter Designation by Defendants

Designation by Defendants

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1 THE UNITED STATES DISTRICT COURT
2 FOR THE DISTRICT OF MASSACHUSETTS
3 JOHN HANCOCK LIFE INSURANCE)
4 COMPANY, JOHN HANCOCK VARIABLE)
5 LIFE INSURANCE COMPANY AND)
6 MANULIFE INSURANCE COMPANY)
7 F/K/A INVESTORS PARTNER)
8 INSURANCE COMPANY)
9)
10 Plaintiff,)
11)
12 VS.) CIVIL ACTION NO:
13) 05-11150-DPW
14 ABBOTT LABORATORIES,)
15)
16 Defendant.)
17 *****
18 ORAL/VIDEO DEPOSITION OF
19 BRUCE RODDA, Ph.D.
20
21 JUNE 6, 2007
22 *****
23
24 HIGHLY CONFIDENTIAL
25

15 ORAL DEPOSITION OF BRUCE RODDA, Ph.D., produced as
16 a witness at the instance of the Plaintiff, was duly
17 sworn, was taken in the above-styled and numbered cause
18 on the JUNE 6, 2007, from 9:00 a.m. to 2:50 p.m., before
19 Chris Carpenter, CSR, in and for the State of Texas,
20 reported by machine shorthand, at the Longhorn
21 Conference Room, Austin Airport Marriot South, 4415 S.
22 IH-35, Austin, Texas, pursuant to the Federal Rules of
23 Civil Procedure and the provisions stated on the record
24 or attached hereto.

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1 testimony cause you to change any of the opinions you
2 expressed in your -- what I'll call your statistical
3 report?

4 A. No, it did not.

5 Q. And just for ease, I'll refer to your rebuttal
6 to Dr. Fairweather as your statistical report and your
7 rebuttal to Dr. Gold as your non statistical report; is
8 that okay?

9 A. Sure. Yes.

10 Q. Did reviewing Dr. Gold's deposition transcript
11 cause you to change any of the opinions that you
12 expressed in your non statistical report?

13 A. No, it did not.

14 Q. When were you engaged by Munger, Tolles & Olson
15 in this matter?

16 A. Earlier this year.

17 Q. In 2007?

18 A. I think so.

19 Q. Who engaged you; which attorney?

20 A. Mr. Phillips.

21 Q. What tasks did Mr. Phillips ask you to do when
22 he engaged you?

23 A. The primary task was to effectively be the
24 external statistical expert on 594, reviewing Dr. Gold's
25 and Dr. Fairweather's initial documents and other

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1 documents associated with this trial from a statistical
2 perspective.

3 Q. Is that it?

4 A. Yes.

5 Q. Was this engagement the first time you had ever
6 worked with the law firm of Munger, Tolles & Olson?

7 A. Yes, it was.

8 Q. What is your understanding about how Munger,
9 Tolles & Olson identified as you an appropriate expert
10 for this case?

11 A. Mr. Phillips told me that I was recommended by
12 an individual at Abbott.

13 Q. Who was that?

14 A. I don't know.

15 Q. Have you done work for Abbott before?

16 A. No.

17 Q. Do you presently have any equity or other
18 interest position in Abbott?

19 A. No, I don't.

20 Q. Have you at any time during the course of your
21 engagement?

22 A. No.

23 Q. Your present rate in this matter is how much?

24 A. \$350 a hour.

25 Q. And from the time you were engaged until today,

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1 companies at which you worked, you would agree that
2 companies evaluate the likelihood of regulatory approval
3 in determining whether to pursue development of drugs,
4 wouldn't you?

5 A. Yes.

6 Q. And you would agree, based on your experience,
7 that companies evaluate the results of clinical trials
8 in deciding whether or not to pursue development of
9 drugs, right?

10 A. That's correct.

11 MR. ZWICKER: Greg, we've been going an
12 hour. You want to take five?

13 MR. PHILLIPS: Sure.

14 MR. ZWICKER: Okay, let's do that. I'm
15 about to move into a new area.

16 VIDEOGRAPHER: We're off the record at
17 10:05 a.m.

18 (recess.)

19 VIDEOGRAPHER: We're back on the record at
20 10:16 a.m.

21 Q. (BY MR. ZWICKER) Dr. Rodda, from a statistical
22 standpoint, can you define the phrase "power" for me?

23 A. Power is the probability that a study will be
24 statistically significant --

25 Q. Your words, not mine.

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1 A. I apologize.

2 -- given some assumptions.

3 Q. In the world of statistics, power is known as a
4 planning tool, correct?

5 A. Primarily, yes.

6 Q. What does it mean to say that power is a
7 planning tool?

8 A. The way I define power, the probability of
9 observing a statistically significant result at the end
10 of the study is used to design a study with certain
11 assumptions and certain sample size so that there will
12 be an understood assurance of success. And by success,
13 I mean a statistically significant difference between
14 the treatment and placebo, if there just an active and
15 control agent in the study.

16 MR. ZWICKER: Okay. Let's go off the
17 record.

18 (Brief recess).

19 VIDEOPHOTOGRAPHER: We're back on the record at
20 10:18 a.m..

21 Q. (BY MR. ZWICKER) Dr. Rodda, is it fair to say
22 that power is a way of maximizing the likelihood that
23 the results of a study will show a statistically
24 significant difference between a drug treatment and
25 placebo; is that accurate?

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1 MR. PHILLIPS: Objection to the form.

2 A. Power is the probability of seeing a
3 statistically significant difference between an active
4 and a placebo.

5 Q. Why is -- why is it important to design trials
6 with a probability of detecting a difference between
7 treatment and placebo?

8 A. Studies are an investment, both financial and
9 in patients. When one begins a study, when one embarks
10 on a study, it is important to understand the risks
11 associated with the study. The study can fail for a
12 variety of reasons. There's no guarantee that any study
13 will be positive. There's -- and power is used to
14 create an index so that the sponsor understands the
15 probability that the study will be a success, given some
16 assumptions.

17 Q. Would you agree that it's a way of maximizing
18 your probability of a conclusive result?

19 MR. PHILLIPS: Object to form.

20 A. I would not use the term maximize. I would use
21 the term quantify.

22 Q. (BY MR. ZWICKER) Fair to say that you testified
23 that clinical trials are expensive, correct?

24 A. Correct.

25 Q. So the sponsor hopes to design a study that

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1 will have a high probability of detecting a desired

2 difference between treatment and placebo, fair?

3 MR. PHILLIPS: Object to the form.

4 A. In general, yes.

5 Q. (BY MR. ZWICKER) And one of the reasons for

6 that objective on behalf of a sponsor like Abbott is you

7 don't want to have to repeat a study, right?

8 MR. PHILLIPS: Object to the form.

9 A. Yes.

10 Q. (BY MR. ZWICKER) In your experience, does --

11 can repeating studies delay development of compounds?

12 A. Yes.

13 Q. You've reviewed several documents relating to

14 the 99-114 study in preparation for today, correct?

15 A. I have.

16 Q. One of the goals of the 99-114 study was to

17 detect statistically significant difference between

18 treatment groups and placebo; is that fair?

19 A. Yes.

20 MR. PHILLIPS: Object to the form.

21 Q. (BY MR. ZWICKER) Is it your understanding that

22 Abbott's objective was to detect a difference or effect

23 size of .46?

24 A. Yes.

25 Q. Can you explain to me what that means?

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1 A. The -- the .46 effect size that Abbott used to
2 design the study was a ratio of the difference in the
3 response of an active group compared with a placebo,
4 divided by the standard deviation. It's a standardized
5 effect size that they used to estimate the size of that
6 study.

7 Q. But that desired effect was Abbott's objective
8 in designing the study?

9 A. When Abbott designed the studied, it is my
10 understanding that they identified that as the effect
11 that they wanted to be sure that they found if it were
12 there. And they designed the study to detect that
13 difference or that treatment effect.

14 Q. In designing the study, Abbott selected a power
15 of 80 percent, correct?

16 A. That's correct.

17 Q. What is your understanding of why it is that
18 Abbott selected 80 percent for the 99-114 study?

19 A. I don't know why they selected 80 percent.

20 Q. Would you agree with me that sponsors in
21 general like Abbott desire a high probability of a
22 conclusive study?

23 MR. PHILLIPS: Objection to the form.

24 A. In general, yes.

25 Q. (BY MR. ZWICKER) And is it also fair to say

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1 that power is a way of planning to avoid an inconclusive

2 study? Would you agree with that?

3 A. I would.

4 Q. Would you also agree that at least Abbott
5 statisticians determined that 80 percent power in this
6 study would provide sufficiently conclusive results?

7 MR. PHILLIPS: On object to the form.

8 A. I don't know who at Abbott decided whether 80
9 percent power was appropriate.

10 Q. (BY MR. ZWICKER) But you agree that Abbott
11 institutionally made that determination in designing
12 this study, correct?

13 A. Apparently.

14 Q. Putting aside oncology drugs, have you ever
15 designed a study, a clinical trial study at less than 80
16 percent power?

17 A. Yes.

18 Q. Have you ever designed a clinical trial for a
19 pain drug like 594?

20 MR. PHILLIPS: Object to the form.

21 A. Yes.

22 Q. (BY MR. ZWICKER) How many times?

23 A. In this particular indication, probably three
24 times in this particular indication.

25 Q. What you do mean by particular indication?

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1 A. Diabetic neuropathy.

2 Q. And for those three studies that you designed,

3 did you select a power below 80 percent?

4 A. No.

5 Q. More than 80 percent?

6 A. In one case.

7 Q. And 80 percent in the other two?

8 A. I think so.

9 Q. Why did you select 80 percent or more in the
10 three that you designed?

11 A. The selection of power is not an individual's
12 selection; it is a strategic decision by the
13 company. So in my case, this was a decision that was
14 reached by all the parties that were responsible for the
15 design of the study.

16 Q. But that strategic decision was informed by a
17 desire to have a conclusive result from the study, true?

18 A. Yes.

19 Q. You used the phrase "sample size" a few moments
20 ago. In order to design a study with 80 percent power
21 to show a .46 effect, Abbott would have had to determine
22 a sample size, correct?

23 A. Correct.

24 Q. What is a sample size?

25 A. A sample size is the number of patients that

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1 are assigned to each of the treatment groups or the
2 totality of the patients that are included in all of the
3 treatment groups.

4 Q. In your opinion, Dr. Rodda, why is it important
5 in designing a clinical trial to select a proper sample
6 size?

7 MR. PHILLIPS: Object to the form. Vague
8 as to "proper."

9 A. The selection of a proper sample size provides
10 the sponsor with an understanding of their risk of
11 success and failure to find a particular treatment
12 effect. If the -- if they use too few patients, that
13 likelihood would decrease. If they use too many
14 patients, they may be spending money and exposing
15 patients unnecessarily.

16 Q. (BY MR. ZWICKER) So sponsors prefer to find the
17 right balance; is that fair?

18 A. That's correct.

19 Q. One of the risks of selecting too few patients
20 for a sample size is a risk that you might have to
21 repeat the study again, true?

22 MR. PHILLIPS: Object to the form.

23 A. That's one of the risks.

24 Q. (By MR. ZWICKER) What are the others?

25 A. That you may not be able to repeat the study or

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1 the study may turn out to be negative.

2 Q. How do you mean negative?

3 A. Inconclusive.

4 Q. By inconclusive, you mean that it doesn't show,

5 for the purposes the 99-114 study by example, it doesn't

6 show the effect that you hoped it would show when the

7 results are in?

8 A. By conclusive, I mean that the -- the

9 statistical significance of the outcome is not

10 definitive enough to make the conclusion that the study

11 was designed to make.

12 Q. And one of the risks of too small a sample size

13 is that you would not be able to draw that conclusion

14 that, fair?

15 A. That's correct.

16 Q. In the 99-114 study, Abbott selected 80 percent

17 power, correct?

18 A. Correct.

19 Q. And that was a decision that Abbott

20 statisticians made, correct?

21 MR. PHILLIPS: Objection, asked and

22 answered.

23 Q. (BY MR. ZWICKER) You can answer.

24 A. It's a corporate -- it's a sponsor's -- excuse

25 me. It's a strategic decision.

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1 Q. Did you yourself, in connection with your
2 testimony today, draw -- attempt to calculate a sample
3 size that would have achieved 80 percent power with a
4 .46 effect?

5 A. Are you asking have I -- did I try to duplicate
6 the Abbott calculations?

7 Q. Correct, that's what I'm asking.

8 A. I did do that.

9 Q. You did or did not?

10 A. I did.

11 Q. And what were your results?

12 A. The same as Abbott's.

13 Q. Which means what?

14 A. That assuming a treatment effect of .46 and a
15 power of .8 and an alpha level Type I error level of
16 .05, that the -- that 80 patients per group, their
17 sample size, would provide 82 percent power for finding
18 the .46 effect significant.

19 Q. As a general statistical matter, if one reduces
20 sample size, is it fair to say that one also reduces
21 power?

22 MR. PHILLIPS: Objection to the form,

23 incomplete hypothetical.

24 A. I want to tie some things together. I want to
25 tie power, sample size, treatment effect and

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1 variability, because it's very difficult and perhaps

2 impossible to talk with one without the other.

3 So to answer your question, if the

4 variability was as hypothesized --

5 Q. Constant.

6 A. No. There is a -- in designing the study,

7 there was an assumption of a particular variability, and

8 Abbott did not know what the true variability would be.

9 They couldn't know. So they had to assume that there's

10 a variability in the system to design the study. When

11 the study is actually implemented, that variability may

12 be greater or less than what they thought it was going

13 to be. And the impact of that will be to increase or

14 decrease the probability of success, depending on the

15 greater the variability, the less likelihood of success

16 given the same sample size.

17 Sample size works the same way. If

18 variability is constant, if we don't think about

19 variability, if we don't think about the treatment

20 effect that we were interested in, increasing sample

21 size increases power. Decreasing sample size decreases

22 power.

23 Q. Abbott didn't know the actual variability of

24 the 99-114 study until it unblinded the data, right?

25 A. That's correct.

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1 Q. Before Abbott unblinded the data, it made
2 certain assumptions about variability, correct?

3 A. I don't know.

4 Q. Well, variability assumptions, as you said,
5 have an impact on sample size, correct?

6 MR. PHILLIPS: You have to answer
7 verbally.

8 THE WITNESS: I'm sorry. I apologize.

9 MR. ZWICKER: Thank you. That's usually
10 my job.

11 A. They had to make some assumptions about
12 variability to design the study, to come up with the
13 sample size in the first place.

14 Q. (BY MR. ZWICKER) Before the results are
15 unblinded and while Abbott's initial assumptions
16 regarding variability are in place, would you agree with
17 me that reducing sample size reduces plan power?

18 A. It would reduce it if the variability were
19 unchanged from what they hypothesized it would be and
20 that the treatment effect was unchanged from what they
21 hypothesized it would be.

22 Q. But again, you only know actual variability
23 once you unblind the data, true?

24 A. True.

25 Q. You agreed Abbott made certain assumptions

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1 enrollment in the 99-114 study as of December 14, 2000,
2 fair?

3 MR. PHILLIPS: Objection, mischaracterizes
4 the document.

5 A. It proposes that they terminate enrollment.

6 Q. (BY MR. ZWICKER) Based on your review of
7 documents in this case, you understood that Abbott had a
8 target enrollment of 320, correct?

9 A. Yes.

10 Q. And do you also understand, based on your
11 review of documents in this case, that the total number
12 of persons randomized to the 99-114 study ultimately was
13 266?

14 A. Yes.

15 Q. Do you agree that as of the date Abbott reduced
16 enrollment from 320 to 266, that Abbott should have
17 known that plan power would have been reduced?

18 A. Probably.

19 Q. Why do you say probably?

20 A. Because of the other factors that they were
21 unaware of which could have affected the power as well,
22 the treatment difference and the variability.

23 Q. Okay. But as of December 2000, Abbott doesn't
24 know the variability, right?

25 A. That's correct.

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1 Q. This is actually one of those examples of where
2 Mr. Phillips happens to be right, rare but true, that
3 we're speaking over one another.

4 MR. PHILLIPS: One of many examples.

5 Q. (BY MR. ZWICKER) And as of December 2000,
6 Abbott hasn't changed the desired effect for the 99-114
7 study, right?

8 A. That's correct.

9 Q. So fair to say that as of December 2000, Abbott
10 should have appreciate that reduction of the sample size
11 from 320 to 266 should reduce plan power, true?

12 MR. PHILLIPS: Objection to the form.

13 A. It may reduce plan power.

14 Q. (BY MR. ZWICKER) But power is a judgment that
15 is made before you actually have results, typically,
16 it's a planning tool, right?

17 A. That's correct.

18 Q. So, as of December 2000, Abbott would have to
19 reduce plan power, wouldn't it?

20 MR. PHILLIPS: Object to the form.

21 A. I think they -- that's a probable yes.

22 Q. (BY MR. ZWICKER) What is your understanding,
23 based on documents you reviewed or conversations that
24 you've had with Mr. Phillips, regarding why it was that
25 Abbott reduced the sample size in the 99-114 study?

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1 A. Assuming that the variability and the treatment
2 effect were as they hypothesized, it would have the
3 effect of reducing the power of the study.

4 Q. (BY MR ZWICKER) And reducing the enrollment
5 size from 320 to 266 effectively reduces the sample size
6 as well, doesn't it?

7 A. I'm sorry. Would you say that again?

8 Q. Yes. Reducing the enrollment target
9 effectively has the result of reducing the sample size,
10 doesn't it?

11 A. I'm sorry. It sounds like a tautology.

12 Q. Let me try it once more.

13 Abbott -- Abbott's objective was for a
14 sample size of 320 persons?

15 A. Correct.

16 Q. At the time enrollment was terminated, 266
17 patients were randomized?

18 A. Correct.

19 Q. Fair to say that the sample size is now been
20 reduced?

21 A. Yes.

22 Q. Do you agree with the proposition that stopping
23 enrollment short of target may result in a study where
24 the treatment difference between the agent and control
25 may not be statistically significant?

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1 MR. PHILLIPS: Object to the form.

2 A. It may not. But it also may not if you

3 completed the study to full enrollment.

4 Q. (BY MR. ZWICKER) What do you mean by completed

5 the study to full enrollment?

6 A. All other assumptions being the same,

7 variability and treatment difference, had the study been

8 conducted through with 320 patients, you would have had

9 a twenty percent chance of an inconclusive result. So

10 the fact that you went through the entire sample,

11 doesn't guarantee that you're going to have a conclusive

12 result.

13 Q. Okay. But reducing -- terminating enrollment

14 increases the probability that the desired effect may

15 not be statistically significant, true?

16 MR. PHILLIPS: Objection to the form.

17 A. It does affect it.

18 Q. (BY MR. ZWICKER) It increases the probability?

19 A. It increases the probability.

20 Q. And by increasing the probability, does

21 reducing the sample size also increase the probability

22 of repeating the trial?

23 MR. PHILLIPS: Objection to the form.

24 Vague as to increasing the probability of what?

25 A. I can't answer that question. That would be a

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1 A. No.

2 Q. You don't know one way or another or you
3 disagree?

4 A. I don't think it was in the protocol stated
5 that way.

6 Q. Based on your experience, and putting yourself
7 in Abbott's shoes as of December 2000, is it -- would it
8 be your opinion that the failure to achieve the
9 enrollment target is a potentially important fact in the
10 development of 594?

11 MR. PHILLIPS: Objection to the form.

12 A. It could be.

13 Q. (BY MR. ZWICKER) Why?

14 A. Because the -- your probability of success is
15 being potentially reduced by reducing the sample size.

16 Q. Could you turn to page 17 of your report. And
17 by your report, I mean Exhibit Number 2.

18 You have on page 17, you reproduced a
19 table, and you have a discussion about the implications
20 of terminating enrollment on power, see that?

21 A. Yes.

22 Q. You say, "It can be seen from this table that
23 the actual number of patients at the termination of
24 enrollment, 266 or about 65 per group, would provide 74
25 percent power to detect the hypothesized .46 treatment

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1 effect compared with an initial power at least 80

2 percent as cited in the protocol." Do you see that?

3 A. Yes.

4 Q. In your opinion, given your review of documents

5 relating to the 99-114 study, do you think a reduction

6 in power from 80 percent to 74 percent is significant?

7 MR. PHILLIPS: Object to the form.

8 A. It depends on the corporate objectives, the

9 risk the company is going to take.

10 Q. (BY MR. ZWICKER) Based on the documents you've

11 reviewed, do you have any opinion regarding the

12 company's view of reducing power from 80 to 74 percent

13 based on cutting the enrollment target?

14 A. No.

15 Q. Dr. Rodda, in studies that you've designed,

16 have there been situations where you view a reduction in

17 power of 6 percent to be significant in the development

18 of a compound?

19 MR. PHILLIPS: Object to the form.

20 A. No.

21 Q. (BY MR ZWICKER) In other words, I want to make

22 sure my question is right, there has never been a

23 situation where you concluded that a reduction of 6

24 percent was meaningful?

25 A. Not that I can recall.

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1 Q. Why is that?

2 A. Can I use an example?

3 Q. Yeah.

4 A. May I refer to Dr. Fairweather's testimony?

5 Q. Sure.

6 A. Recall in that testimony, there was a question

7 of changing the variability by ten percent from 1 to

8 1.1, increasing the variability by just ten percent. By

9 doing that, the effect on power is exactly the same as

10 reducing the sample size from 320 to 266.

11 The variability estimates that go into

12 designing a clinical trial are in fact estimates. If

13 the variability is 1 and I estimated it as a .9 or 1.1,

14 that is -- that's pretty accurate. So that the

15 proximations that go into estimating a sample size,

16 if -- if the difference between 1 and 1.1 would make

17 this much difference, then the reduction of a sample

18 size providing an equivalent difference in power, has to

19 be taken with that into consideration.

20 So, a small decrease in power like this is

21 not something that, in my experience, would have been

22 viewed as being a critical reduction.

23 Q. Are you saying that for the 99-114 study,

24 Abbott assumed a range of variability in calculating

25 sample size?

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1 A. I don't know that.

2 Q. Wouldn't you have to know the range of
3 variability assumed in order to assess the impact of a 6
4 percent reduction in power?

5 A. No.

6 Q. Why not?

7 A. If you -- when interpreting the impact on these
8 reductions in power or changes in variability -- excuse
9 me -- reductions in sample size or changes in
10 variabilities or changes in target treatment effects,
11 these are often compared in pairs to determine the
12 impact of one on the other, and in designing a study,
13 one knows that the estimates are in fact estimates, and
14 sensitivity may be assessed at that time.

15 There was no evidence in what I read that
16 Abbott wanted to reconsider their variability nor
17 reconsider their treatment effect, but were only
18 interested, given that those had not -- were not
19 changing the impact of their sample size reduction on
20 the power of their study.

21 Q. So is it your testimony that Abbott assumes
22 certain -- made certain assumptions about variability in
23 the 99-114 study; is that right?

24 A. Yes.

25 Q. And what is the relationship between those

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1 variability assumptions and a reduction in power?
2 A. If the assumed variability is incorrect, if it
3 is too low, then the power will be reduced. If the
4 variability that they assumed is too high and that the
5 true variability is lower, then the power will be
6 increased for the same sample size.

7 Q. But at this point in December 2000, Abbott as
8 you've testified, doesn't know what the variability is
9 going to be?

10 A. That's true.

11 Q. So is Abbott in a position to assess the impact
12 of a reduction in power of 80 to 74 percent without
13 knowing what the variability is going to be?

14 A. The impact in terms of power?

15 Q. Yeah.

16 A. They -- they could speculate what the impact
17 would be with different variabilities.

18 Q. But they don't know?

19 A. But they don't know.

20 Q. Is there a reduction in power in studies you've
21 done that you would consider to be extremely significant
22 in determining whether a study will be conclusive or
23 not?

24 MR. PHILLIPS: Objection to the form.

25 A. In general -- in general, no. The concerns

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1 about lack of enrollment were either for a reason that
2 power then became moot or that the enrollment was
3 acceptable in terms of an adequate power. And adequate
4 is -- I won't define that because it's -- adequate means
5 acceptable to the sponsor in that case.

6 Q. (BY MR ZWICKER) Would you consider a reduction
7 in power to, say, 65 percent to be significant in the
8 99-114 study?

9 MR. PHILLIPS: Object to the form.

10 A. I think the reduction of power from 82 percent
11 to any point afterward is one that depends on a number
12 of factors, and I would just -- I would be speculating
13 without having knowledge of those factors.

14 One of the things that I would like to
15 point out is that the reduction of power from 80 percent
16 to 75 percent, say, still means that there's a three-to-
17 one chance that the study will be successful. Reducing
18 it to 67 percent means there's a two-to-one chance that
19 the study will be successful. Those are still high
20 odds, and it would be a corporate decision about where
21 the cutoff point came, where the risk of failure was not
22 worth the benefit.

23 Q. (BY MR ZWICKER) In your experience, have you
24 planned most clinical trials with 80 percent power?

25 A. I would say that many late Phase 2 and Phase 3

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1 studies are planned with 80 percent power, but I want to
2 again link the -- the concept of treatment effect and
3 variability, because in many studies the sponsor will
4 say, "We'd like to have 80 percent power and we can
5 afford 100 patients. What difference can we detect?"
6 So separating power from the treatment
7 effect, they are not separable. They are linked. And
8 you saw the equation in my report. If you change one,
9 you change the others. So you can always fix one. You
10 always fix it to be 80 percent power and then vary your
11 treatment effect, vary your variability, vary your
12 sample size. Now, there's no evidence that Abbott did
13 that. But that's why I want to emphasize you can't just
14 separate power from sample size.

15 Q. But I think your testimony is that in most of
16 the -- at least initially for the studies that you
17 planned, you selected 80 percent power or better?

18 A. On many of them, not most of them. Early
19 studies -- early studies are often done with less than
20 80 percent power.

21 Q. But Phase 2 trials are mostly done with 80
22 percent power?

23 A. Late Phase 2 and Phase 3 trials are usually
24 done with higher powers.

25 Q. This is a late Phase 2 trial, right?

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1 A. Potentially.

2 Q. Why only potentially?

3 A. Because if a patient drops out of a study for a
4 specific reason, for example, tolerability or lack of
5 efficacy, that provides information. And if they drop
6 out, for example, for tolerability reasons, that
7 provides information that may not be attainable if they
8 completed the study.

9 Q. In your experience, does the FDA consider the
10 reasons why patients drop out of clinical trials?

11 A. Yes.

12 Q. What do they look at?

13 MR. PHILLIPS: Object to the form.

14 A. They are interested in -- if there is an
15 association for the reason for dropping out and the
16 therapies under study.

17 Q. (BY MR. ZWICKER) And to the extent that there
18 is an association for the reasons people drop out and
19 the treatment, that's a factor that is not helpful to
20 the development of the compound?

21 MR. PHILLIPS: Object to the form. I'm
22 not -- object, vague.

23 A. The purpose of any clinical trial is to
24 characterize both the safety and efficacy. If patients
25 drop out for safety reasons, that is part of the

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1 characterization of the safety profile. Whether it's
2 desirable or not is a different issue.

3 Q. (BY MR. ZWICKER) For a drug like 594, is it
4 your opinion that the FDA would treat dropouts for
5 adverse effects in a negative way, given the nature of
6 the drug?

7 MR. PHILLIPS: Objection.

8 A. I'm not sure what you mean by -- treat in a
9 negative way.

10 Q. (BY MR. ZWICKER) 594 was a pain drug, correct?
11 A. Yes.

12 Q. In your opinion, is the FDA more insistent that
13 pain drugs have fewer adverse effects than other kinds
14 of drugs?

15 MR. PHILLIPS: Objection, form.

16 A. I would be speculating about what the FDA
17 feels.

18 Q. (BY MR. ZWICKER) Okay. But it is your
19 testimony that the FDA does scrutinize the relationship
20 between adverse events and a treatment, correct?

21 A. Yes, that's true.

22 Q. You've reviewed the protocol for 99-114,
23 haven't you?

24 A. I did.

25 Q. What is -- based on -- well, why don't we mark

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1 it.

2 (Exhibit 5 marked for identification).

3 Q. (BY MR. ZWICKER) Dr. Rodda, before the witness
4 is the Abbott Laboratories clinical protocol for 99-114,
5 dated February 8, 2000, and bears Bates numbers 65818
6 through 65896.

7 Dr. Rodda, do you recognize this as the
8 protocol that you reviewed?

9 A. Yes.

10 Q. Take a look at page -- it's 40 of the protocol
11 and it bears Bates Number 65869. Do you see that? It
12 says Data Sets Analyzed?

13 A. Yes.

14 Q. Can you review that to yourself and let me know
15 when you're done?

16 MR. PHILLIPS: Just that one paragraph?

17 MR. ZWICKER: Just that one paragraph.

18 A. Okay. I'm done.

19 Q. (BY MR. ZWICKER) You're done? Can you tell me,
20 based on this protocol, what an intent-to-treat analysis
21 is?

22 A. An intent-to-treat analysis is designed to
23 include as many patients as possible in the final
24 analysis, so that patients are not excluded for reasons
25 that -- for events that happened to them during the

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1 conduct of the study. The intent-to-treat analysis in
2 general includes all patients randomized to treatment
3 that had any information that addresses the specific
4 objective.

5 Q. What is the valuable data within the context of
6 this protocol?

7 A. They have defined their intent-to-treat set as
8 patients who will receive one dose of study drug, had a
9 baseline, and had at least one followup pain assessment.

10 Q. So based on this protocol, sir, it's your
11 conclusion that the intent-to-treat dataset is the
12 evaluable dataset?

13 MR. PHILLIPS: Objection, mischaracterizes
14 the testimony.

15 A. No. No. The dataset -- that evaluable dataset
16 is different. The evaluable dataset requires a week of
17 therapy, seven days of study drug. The intent-to-treat
18 requires one does of study drug.

19 Q. And both evaluable date and the intent-to-treat
20 datasets are used in analyzing the results once they're
21 known?

22 A. In general, yes.

23 Q. Was that true here?

24 A. They used an intent-to-treat approach and they
25 used an observed-cases approach in their evaluation of

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1 efficacy.

2 Q. For an intent-to-treat analysis, an intent-to-
3 treat analysis assumes that certain subjects, certain
4 enrolled subjects are going to prematurely terminate,
5 correct?

6 A. It doesn't assume that. If that happens, then
7 their information will still be included in the
8 analysis. They will not be excluded.

9 Q. In the intent-to-treat analysis for the 99-114
10 protocol, is Abbott going to infer data on how the
11 patients would have done had they completed the
12 protocol?

13 A. Abbott used a technique called last observation
14 carried forward, which imputed the last observation, the
15 last pain observation for patients who dropped out
16 through what -- through their visit schedule, had they
17 completed the study.

18 Q. So the intent-to-treat analysis at Abbott used
19 for 99-114 imputes data to subjects that prematurely
20 terminate; is that fair?

21 A. There were -- I think there were two separate
22 analyses, both of which could be called intent-to-treat
23 because they included all the patients, but you're
24 correct in that one of them did impute data for patients
25 who dropped out, efficacy data.

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1 Q. And the other was the safety --

2 A. The other was the observed cases where data

3 were not imputed but all cases were included, or all the

4 patients defined in the population were included.

5 Q. So as you say, data was imputed for the

6 efficacy analysis?

7 A. For one of the efficacy analyses.

8 Q. The primary?

9 A. The primary efficacy analysis.

10 Q. And that's the Likert test, right?

11 A. That's the variable that was used for the

12 primary variable?

13 Q. The Likert scale?

14 A. The Likert scale. It's not a test, it's a

15 scale; it's an evaluation scale.

16 Q. You would agree with me that you would rather

17 actually, as a sponsor, have the data than impute it for

18 efficacy purposes?

19 A. I think good science would require that you

20 have as much evaluable data as possible.

21 Q. I appreciate that, but if given your druthers,

22 wouldn't you rather have actual data from a patient that

23 completed the protocol than imputed data?

24 A. Yes.

25 Q. Dr. Rodda, in your report -- actually now I'm

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1 agreement that's the subject of this litigation, okay?

2 A. (Witness nods head yes.)

3 Q. Would you agree with me that as of March the
4 12th, 2001, that Abbott knew that roughly half of the
5 enrollees in the 99-114 study had prematurely
6 terminated?

7 MR. PHILLIPS: Objection to the form.

8 A. I don't know exactly what they knew at that
9 point.

10 (Exhibit 6 marked for identification.)

11 Q. (By MR. ZWICKER) Before the witness is Exhibit
12 Number 6, which is an e-mail and chart that bears Bates
13 numbers 238329 through 238833.

14 Dr. Rodda, can you review this document
15 and tell me if you recognize it?

16 A. Yes, I do.

17 Q. And do you recognize it as one of the documents
18 that was provided to you in connection with your work
19 today?

20 A. I would have to check the list, but I think so.

21 Q. Yeah. I'll just represent to you that page 2
22 of the statistical report indeed lists this document.

23 A. Thank you.

24 Q. The date on this document is February 27, 2001,
25 which I'm sure you and Mr. Phillips and I could agree is

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1 before March the 12th, 2001. Do you see that?

2 A. Yes.

3 Q. Take a look at page 330.

4 A. Uh-huh, yes.

5 Q. And look at the chart there. Do you see Total

6 Randomized as of 1/04?

7 A. Yes.

8 Q. It says 269; do you see that?

9 A. Yes.

10 Q. That number ultimately became 266, didn't it?

11 A. Apparently.

12 Q. And then to the chart to the right, where it

13 says Early Terminations, and it looks like it says as of

14 2/20, it says 132. Do you see that?

15 A. I see that, yes.

16 Q. And then to the right of that, it says

17 Completed Subjects as of 2/20, and then says 130.

18 A. Yeah.

19 Q. So based on your review of this document, would

20 you agree with me that as of March the 12th that Abbott

21 knew that roughly -- and I think the early termination

22 number is 49 percent -- that Abbott knew that roughly 50

23 percent of the enrollees had prematurely terminated?

24 MR. PHILLIPS: Object to the form.

25 A. It looks that way, yes.

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1 this table is complete, yes.

2 Q. (BY MR. ZWICKER) And I'm just going ask you to
3 assume that there are tables that reflect all the
4 patients involved in the study and the dates they
5 terminated.

6 A. Okay.

7 MR. PHILLIPS: If that was a question,
8 I'll object to the form.

9 MR. ZWICKER: Okay. It wasn't, but you
10 can object.

11 Q. (BY MR. ZWICKER) So you would agree with me
12 that as of February the 27th, Abbott knows that it's not
13 going to have complete data from all 266 enrollees,
14 right?

15 MR. PHILLIPS: Object to the form.

16 A. Yes.

17 Q. (BY MR. ZWICKER) And that it would have to
18 impute under an ITT analysis data for the premature
19 terminations, correct?

20 A. For one of the ITT analyses.

21 Q. For the primary efficacy analysis.

22 A. (Witness nods head yes.)

23 Q. Dr. Rodda, would you agree with me that for
24 purposes of this study, that having to infer data for
25 roughly half the enrollees potentially increases the

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1 variability around the mean?

2 A. No -- sorry.

3 MR. PHILLIPS: I was just objecting to the
4 form.

5 A. No.

6 Q. (BY MR. ZWICKER) Why not?

7 A. If a patient drops out of the study, for
8 example, on day 7, and a value needs to be imputed for
9 the remainder of the study, it's the same number that
10 would be imputed for each of the subsequent visits.
11 It's going to reduce the variability, not increase the
12 variability if the same number is being given through
13 for the remainder of the study.

14 Q. (BY MR. ZWICKER) When Abbott designed the
15 99-114 protocol, do you understand that it made -- that
16 it took account for premature terminations in assuming
17 variability?

18 A. That wasn't clear in the protocol.

19 Q. You couldn't tell?

20 A. No.

21 Q. Would you have expected it to be clear in the
22 protocol?

23 A. Yes.

24 Q. Do you have any understanding why an assumption
25 for variability wasn't in the protocol?

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1 You agreed with me earlier that it's
2 preferable to have someone complete a study than
3 prematurely terminate it, right?
4 A. The more information that a patient provides,
5 the more valuable that patient is.

6 Q. Is it problematic to you to treat, under an ITT
7 analysis, to treat the data of a premature terminator
8 and a completer the same way?

9 MR. PHILLIPS: Object to the form.
10 A. You are combining patients who provide a
11 substantial amount of information with those who may
12 not, but one approach that Abbott did use was the
13 observed cases approach where all patients data,
14 whether it was in -- was used and there was no
15 imputation. I'm not sure whether that answers your
16 question or not, but let me stop there and let you
17 re-ask the question if I haven't answered it properly.

18 Q. (BY MR. ZWICKER) For purposes of the 99-114
19 study, should Abbott have made any adjustments to
20 assumed variability based on the fact that half of the
21 enrollees didn't complete the study?

22 MR. PHILLIPS: Object to the form. Vague
23 as to time.

24 Q. (BY MR. ZWICKER) Let me actually address one
25 of his objections. Prior to March the 12th, 2001,

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1 should Abbott have made any adjustments to variability

2 based on the fact that half the persons enrolled in the

3 study didn't complete it?

4 A. I don't know how they would have.

5 Q. Why not?

6 A. I don't know how they would have.

7 Q. You think they couldn't have?

8 A. I'm saying that I don't know how you would,

9 even if you wanted to, how you would do that. I don't

10 know of any technique to do that.

11 Q. Does the fact that Abbott received incomplete

12 data from roughly half the enrollees in the 99-114 study

13 have any impact on the sample size, again, prior to the

14 March 12, 2001?

15 MR. PHILLIPS: Object to the form.

16 Q. (BY MR. ZWICKER) Do you understand my

17 question?

18 A. Let me try to answer it and see whether I do.

19 The intent-to-treat approach presumes

20 complete data on all patients. So if that is the

21 primary population for analysis, there are effectively

22 no dropouts. And even though much of that data may be

23 imputed, the data is complete. That is, as we -- I

24 testified earlier, that isn't as desirable as having

25 more complete data on individual patients, but Abbott

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1 could view this from the point of view that an intent-
2 to-treat approach was being taken and, because of that,
3 there are few if any dropouts from that analysis, and
4 thus, the sample size is adequate as it is.

5 Q. In your experience where you have had trials
6 with substantial dropout rates, have you made
7 adjustments to sample size to accommodate for the
8 premature terminations?

9 A. No.

10 Q. Why not?

11 A. For the reason that I gave, is that these were
12 -- these were intent-to-treat analysis primarily, and
13 that with substantial dropouts, the -- well, let me just
14 stop there. That there was no support for increasing
15 the sample size if the information available was
16 addressing the question.

17 Q. Do you view a 50 percent dropout rate for the
18 study to be substantial?

19 MR. PHILLIPS: Object to the form.

20 A. It is a high dropout rate.

21 Q. (BY MR. ZWICKER) If you were overseeing the
22 study, would you be concerned about the rate of
23 dropouts?

24 A. I certainly would investigate the rate of
25 dropouts and the reasons for them.

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1 Q. In your experience, have you been able to draw

2 any preliminary conclusions regarding the reasons for
3 dropouts even where data is blinded?

4 A. No, not where data is blinded.

5 Q. Do you believe that the power for the 99-114
6 study should have been further adjusted based on the
7 fact that Abbott knew they had incomplete data from
8 roughly one half of the enrollees?

9 MR. PHILLIPS: Objection to the form.

10 A. No.

11 Q. (BY MR. ZWICKER) Why?

12 A. According to the protocol, this intent-to-treat
13 approach accommodated all the patients and, therefore,
14 the number of patients who were not part of the intent-
15 to-treat analysis was not as small as the number of
16 patients who completed the study and, therefore, the
17 power would be more associated with the sample size of
18 the 266 patients that were enrolled rather than the
19 130-something patients that actually completed the
20 study.

21 Q. (BY MR. ZWICKER) So it's your view that power
22 should not have been further reduced, notwithstanding
23 the fact that data would have to be imputed for roughly
24 half the patients that were enrolled?

25 A. Abbott could consider that there may be an

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1 been desirable or not might have been interesting, but I
2 certainly wouldn't have known how to do it.

3 Q. Will you agree that this was an important study
4 in the development of 594, correct?

5 A. I think it was.

6 Q. And would you agree that it was important for
7 Abbott to understand what impact the premature dropout
8 rate had on its objectives for the trial?

9 MR. PHILLIPS: Objection to the form.

10 A. I think it was certainly something that they
11 were interested in.

12 Q. (BY MR. ZWICKER) But based on your review of
13 the records, it's not a calculation they ever undertook,
14 correct?

15 MR. PHILLIPS: Objection to the form.

16 A. From what I've seen, they did not calculate the
17 impact of the premature dropouts on the ultimate outcome
18 prior to unblinding.

19 Q. (BY MR. ZWICKER) Given the importance of the
20 study, is that a calculation that you would have
21 undertaken if you were running this clinical trial, sir?

22 A. No, I probably wouldn't have.

23 Q. Why?

24 A. Two points. One, as I mentioned before, I
25 don't -- I wouldn't know how to do it. And secondly,

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1 and March 12th is 16 days roughly, right?

2 A. Uh-huh.

3 Q. Do you believe that within 16 days that Abbott
4 would have known the intent-to-treat population?

5 MR. PHILLIPS: Objection.

6 A. I don't know.

7 Q. (BY MR. ZWICKER) But would you agree -- let's
8 assume that, since you are testifying here as an expert,
9 if Abbott did know the intent-to-treat population as of
10 March 12th, it would know that it had 225 patients to
11 evaluate for the primary efficacy variable, correct?

12 MR. PHILLIPS: Objection, form.

13 A. If they did know that -- the intent-to-treat
14 population, then they would know -- would have known
15 that they had 225 patients by their definition.

16 Q. (BY MR. ZWICKER) It's fair to say that if
17 Abbott's intent-to-treat population was 225, but that's
18 also its sample size for the purpose of the 99-114
19 study, true?

20 MR. PHILLIPS: Objection to the form.

21 Q. (By MR. ZWICKER) For purposes of the primary
22 efficacy?

23 A. Yes. That was the sample size used in that
24 analysis.

25 Q. So as of March 12th, Abbott knew that power

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1 knew that its maximum sample size was 225, correct?

2 MR. PHILLIPS: Objection.

3 A. They may have.

4 Q. (BY MR. ZWICKER) And if they did, that would

5 have had an impact on power, true?

6 MR. PHILLIPS: Objection to the form.

7 A. It could have.

8 Q. (By MR. ZWICKER) It would have -- it could have

9 reduced it, correct?

10 A. It could have.

11 Q. And assuming that each of the four arms were

12 equally distributed between the four treatment groups,

13 that comes out to roughly 56 persons per arm?

14 A. (Witness nods head yes.)

15 Q. True?

16 A. Yes.

17 MR. PHILLIPS: Object to the form.

18 Q. (BY MR. ZWICKER) Go back to exhibit -- go back

19 to your report, which is Exhibit 2 on Page 17 and look

20 at Page 17 of your chart.

21 A. Uh-huh. Yes.

22 Q. At a sample size of 55 persons with an

23 effective .46, power to be .67. Do you see that?

24 A. That's correct. Yes.

25 Q. In your opinion, is a power of .67 a

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1 significantly lower power than what the study should
2 have had?

3 MR. PHILLIPS: Object to the form.

4 Incomplete hypothetical.

5 A. Well, the study was designed for 80 for that
6 difference, so anything less than 80 would be reduced.

7 The actual importance of that again is a decision that's
8 based on other factors rather than just this.

9 Q. (BY MR. ZWICKER) But would you agree that --
10 with a plan power of 80 percent and a power of 67
11 percent as of March 12th, that this study would have
12 been underpowered?

13 MR. PHILLIPS: Object to the form.

14 A. Not necessarily.

15 Q. (BY MR. ZWICKER) Why not?
16 A. Because if the true treatment difference were
17 greater than .46, it would have been very well
18 powered. If the variability were less than
19 hypothesized, it could have been very well powered.
20 There are knowns that would prohibit me from stating
21 that the study was underpowered.

22 Q. But you don't know what the true variability is
23 until data is unblinded, correct?

24 A. Frankly, you never know what the true
25 variability is. You only know what was observed in the

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1 study.

2 Q. But you wouldn't know what was observed in the
3 study until the study is unblinded, correct?

4 A. True.

5 Q. And assuming the effect size was .46 -- keep
6 that assumption, okay -- would you agree that if you
7 didn't know what the variability was going to be and you
8 have an effect size of .46, that the study would have
9 been significantly underpowered as a Phase 2B study at
10 65 percent?

11 MR. PHILLIPS: 65 percent we're now going
12 to? Objection.

13 Q. (BY MR. ZWICKER) 67 percent.

14 MR. PHILLIPS: Objection to the form. I
15 didn't know if that was a trick question. Object to the
16 form.

17 A. I would conclude that the power was less than
18 80 percent. I'm loathe to use the term "underpowered."
19 There are too many variables for me to make that
20 conclusion.

21 Q. (BY MR. ZWICKER) Would you have ever -- have
22 you ever designed a Phase 2B trial with a 67 percent
23 power?

24 MR. PHILLIPS: Object to the form.

25 A. I'd like to answer that by going back to a

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1 comment that I made earlier, is that in studies that
2 I've worked on in the past on several occasions, if my
3 client said we would like to find a, for example, a .46
4 difference with a hundred patients, and I said, well,
5 that would give you 67 percent power, and he said, well,
6 I want 80 percent power, so we change the difference.

7 So the question -- the power cannot be
8 divorced from the difference -- the treatment effect and
9 the variability. That's why I say that you can -- it's
10 lower, but underpowered is an opinion.

11 Q. (BY MR. ZWICKER) Okay. If your client came to
12 you and said, "I want .46 effect and a sample size of
13 225," you would tell them that you would have a 67
14 percent power?

15 A. I would say that, yes.

16 MR. ZWICKER: Why don't we break?

17 VIDEOGRAPHER: We're off the record at
18 12:16 p.m.

19 (Lunch recess.)

20 THE VIDEOGRAPHER: We're back on the
21 record at 1:10 p.m.

22 Q. (BY MR. ZWICKER) Good afternoon, Dr. Rodda.

23 A. Good afternoon.

24 Q. This morning I think you testified that you
25 couldn't find any adjustment for premature terminations

Rodda, Bruce (Linked) 6/6/2007 9:00:00 AM

1 SIGNATURE AND CHANGES

2 RE: JOHN HANCOCK VS. ABBOTT LABORATORIES

3 PAGE LINE CHANGE REASON

4 _____

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19 _____

20 I, BRUCE RODDA, Ph.D., have read the foregoing

21 deposition and hereby affix my signature that same is

22 true and correct, except as noted above.

23 _____

24 _____

BRUCE RODDA, Ph.D.

25

Rodda, Bruce (Linked) 6/6/2007 9:00:00 AM

1 THE STATE OF _____)

2 COUNTY OF _____)

3

4 Before me, _____, on this day

5 personally appeared BRUCE RODDA, Ph.D., known to me (or

6 proved to me under oath or through_____

7 (description of identity card or other document) to be

8 the person whose name is subscribed to the foregoing

9 instrument and acknowledged to me that they executed the

10 same for the purposes and consideration therein

11 expressed.

12 Given under my hand and seal of office

13 this _____ day of _____, 2007.

14

15

16 _____

NOTARY PUBLIC IN AND FOR

17 THE STATE OF _____

18

19

20

21

22

23

24

25

Rodda, Bruce (Linked) 6/6/2007 9:00:00 AM

1 THE UNITED STATES DISTRICT COURT
2 FOR THE DISTRICT OF MASSACHUSETTS

3 JOHN HANCOCK LIFE INSURANCE)
4 COMPANY, JOHN HANCOCK VARIABLE)
5 LIFE INSURANCE COMPANY AND)
6 MANULIFE INSURANCE COMPANY)
7 F/K/A INVESTORS PARTNER)
8 INSURANCE COMPANY)
9 Plaintiff,)
10 VS.) CIVIL ACTION NO:
11) 05-11150-DPW
12 ABBOTT LABORATORIES,)
13)
14 Defendant.)

15 *****
16 CERTIFICATE FROM THE
17 ORAL DEPOSITION OF BRUCE RODDA, Ph.D.
18 JUNE 6, 2007
19 *****

20 I, Chris Carpenter, Certified Shorthand
21 Reporter in and for the State of Texas, do hereby
22 certify that the foregoing deposition is a full, true
23 and correct transcript;

24 That the foregoing deposition of BRUCE
25 RODDA, Ph.D., the Witness hereinbefore named, was at the
26 time named, taken by me in stenograph on JUNE 6, 2007,
27 the said Witness having been by me first duly cautioned
28 and sworn to tell the truth, the whole truth, and
29 nothing but the truth, and the same was thereafter
30 reduced to printed transcript by me or under my
31 direction. The charge for the completed deposition is
32 \$_____ due from Plaintiff;

Rodda, Bruce (Linked) 6/6/2007 9:00:00 AM

1 () That pursuant to the Federal Rules of Civil
2 Procedure, the Witness shall have 30 days after being
3 notified by certified mail, return receipt requested, by
4 the deposition officer that the original deposition
5 transcript is available in his office for review and
6 signature by the Witness and if any corrections made are
7 attached hereto;

8 () That by agreement of counsel, a reading
9 condensed copy of the deposition transcript along with
10 the full-size original Changes and Signature Sheet has
11 been sent to _____ on _____
12 for review and signature within 30 days and if any
13 corrections returned are attached hereto;

14 () That by agreement of counsel, the
15 deposition officer is instructed to release the original
16 deposition transcript, and the deposition officer is
17 thereafter released of any further responsibility with
18 regard to the original.

19 () That the signed transcript () was () was not
20 received from the Witness within 30 days.

21 () That the examination and signature of the
22 Witness is waived by the Witness and the parties.

23 () That the amount of time used by each party at
24 the deposition is as follows:

25 MR. ZWICKER: 4 hours, 24 minutes

Rodda, Bruce (Linked) 6/6/2007 9:00:00 AM

1 I further certify that I am neither counsel for,
2 related to, nor employed by any of the parties in the
3 action in which this proceeding was taken, and further
4 that I am not financially or otherwise interested in the
5 outcome of the action.

6 WITNESS MY HAND, this the _____ day of
7 _____, A.D. 2007.

8

9

10 Cert. NO. 1151

Expires: Dec. 31, 2008 _____

11 (512)328-5557 Chris Carpenter

Certified Shorthand Reporter

12 in and for the State of Texas

13

14

15

16

17

18

19

20

21

22

23

24

25

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 OF COUNSEL

E. LEROY TOLLES
 RETIRED

WRITER'S DIRECT LINE
 (213) 683-9196
 (213) 683-4096 FAX
 Ozge.Guzelsu@mto.com

July 13, 2007

VIA FACSIMILE AND U.S. MAIL

Joseph H. Zwicker, Esq.
 Choate Hall & Stewart LLP
 Two International Place
 Boston, MA 02110

Re: John Hancock Life Ins. Co., et al. v. Abbott Laboratories

Dear Mr. Zwicker:

Bruce Rodda signed the original transcript of his June 6, 2007 deposition. The corrections made are as follows:

Page/Line Number	Change	Reason
Page 44, line 18	Change "statistic" to "statistics"	Typo
Page 59, line 2	Change "with" to "about"	Clarification
Page 59, line 14	Remove "depending on" and insert "--"	Clarity
Page 62, line 24	After "I think it is." begins Mr. Zwicker's next question.	Correction
Page 63, line 5	Remove "the"	Clarity
Page 64, line 10	Change "appreciate" to "appreciated"	Typo

MUNGER, TOLLES & OLSON LLP

Joseph H. Zwicker

July 13, 2007

Page 2

Page/Line Number	Change	Reason
Page 64, line 13	Change "plan" to "planned"	Typo
Page 64, line 19	Change "plan" to "planned"	Typo
Page 71, line 1	Remove a "one"	Typo
Page 74, line 15	Change "proximations" to "approximations"	Typo
Page 75, line 18	Replace ", given that those had not -- were not changing" with "in"	Clarification
Page 78, line 10	Remove "always"	Clarification
Page 83, line 18	Change "does" to "dose"	Typo
Page 83, line 19	Change "date" to "dataset"	Typo
Page 84, line 15	After the word "out" insert "as their imputed pain observation for the remainder of the study." Delete lines 16 and 17.	Clarification
Page 92, line 6	Change "given" to "provide"	Clarity
Page 92, line 15	Change "primarily" to "primary"	Typo
Page 93, line 14	Remove ", whether it was in --"	Clarity
Page 97, line 8	Change "equivalence" to "equivalents"	Typo
Page 98, line 2	Change "plan" to "planned"	Typo
Page 98, line 10	Change "plan" to "planned"	Typo
Page 98, line 15	Change "to" to "from"	Clarity
Page 98, line 24	Change "to be" to "be to"	Typo
Page 107, line 13	Replace "as" with "is a"	Typo
Page 107, line 21	Remove "to"	Typo
Page 109, line 4	Replace "leave" with "least"	Typo
Page 113, line 20	Replace "knowns" with "unknowns"	Typo

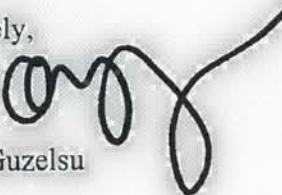
MUNGER, TOLLES & OLSON LLP

Joseph H. Zwicker
 July 13, 2007
 Page 3

Page/Line Number	Change	Reason
Page 114, line 18	Replace "loathe" with "loath"	Typo
Page 131, line 10	Delete lines 10 and 11 after the word tolerability and replace with "and adverse events."	Clarification
Page 133, line 13	Insert the word "and" after the word "groups"	Clarity

Copies of the signature page and the errata sheets are included with this letter. Please do not hesitate to call if you have any questions or comments.

Sincerely,



Ozge Guzelsu

cc: Richard C. Abati, Esq. (w/encl.)
 Jeffrey I. Weinberger, Esq. (w/encl.)
 Gregory D. Phillips, Esq. (w/encl.)
 Eric J. Lorenzini, Esq. (w/encl.)
 Brian A. Davis, Esq. (w/encl.)
 Karen Collari Troake, Esq. (w/encl.)
 Andie Cardinale (w/encl.)
 Kathy Herrity (w/encl.)

HIGHLY CONFIDENTIAL

Page 153

1

SIGNATURE AND CHANGES

2

RE: JOHN HANCOCK VS. ABBOTT LABORATORIES

3

PAGE LINE CHANGE

REASON

4

Please see pages 153A, 153B, 153C

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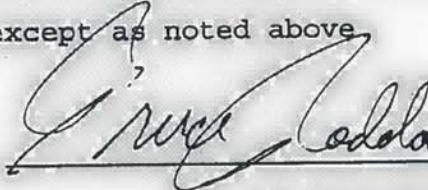
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19

20 I, BRUCE RODDA, Ph.D., have read the foregoing
21 deposition and hereby affix my signature that same is
22 true and correct, except as noted above.

 7/10/07

BRUCE RODDA, Ph.D.

25

HIGHLY CONFIDENTIAL

Page 153

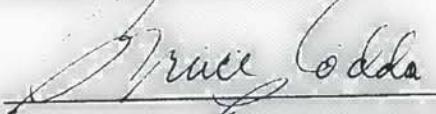
A

SIGNATURE AND CHANGES

RE: JOHN HANCOCK VS. ABBOTT LABORATORIES

PAGE	LINE	CHANGE	REASON
44	18	Change "statistic" to "statistics" - typo	
59	2	Change "with" to "about" - clarification	
59	14	Remove "depending on" insert " - " clarity	
62	24	After "I think it is." begins Mr. Zwicker's next question. - Correction	
63	5	Remove "the" - clarity	
64	10	Change "appreciate" to "appreciated" - typo	
64	13	Change "plan" to "planned" - typo	
64	19	Change "plan" to "planned" - typo	
71	1	Remove a "one" - typo	
74	15	Change "proximations" to "approximations" - typo	
75	18	Replace ", given that those had not -- were not changing" with "in" - clarification	
78	10	Remove "always" - clarification	
83	18	Change "does" to "dose" - typo	
83	19	Change "date" to "dataset" - typo	

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 22 true and correct, except as noted above.

 7/10/07

BRUCE RODDA, Ph.D.

25

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Page 153

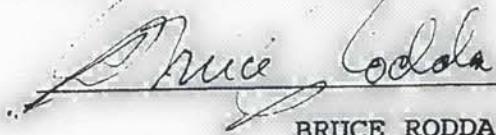
B

1 SIGNATURE AND CHANGES

2 RE: JOHN HANCOCK VS. ABBOTT LABORATORIES

PAGE	LINE	CHANGE	REASON
84,	15	After the word "out" insert "as their imputed pain observation for the remainder of the study." Delete lines 16 and 17.	- classification
92,	6	Change "given" to "provide" - clarity	
92,	15	Change "primarily" to "primary" - typo	
93,	14	Remove ", whether it was in --" - clarity	
97,	8	Change "equivalence" to "equivalents" - typo	
98,	2	Change "plan" to "planned" - typo	
98,	10	Change "plan" to "planned" - typo	
98,	15	Change "to" to "from" - clarity	
98,	24	Change "to be" to "be to" - typo	
107,	13	Replace "as" with "is a" - typo	
107,	21	Remove "to" - typo	
109,	4	Replace "leave" with "least" - typo	
113,	20	Replace "knowns" with "unknowns" - typo	

20 I, BRUCE RODDA, Ph.D., have read the foregoing
 21 deposition and hereby affix my signature that same is
 22 true and correct, except as noted above.


 7/10/07

BRUCE RODDA, Ph.D.

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Page 153

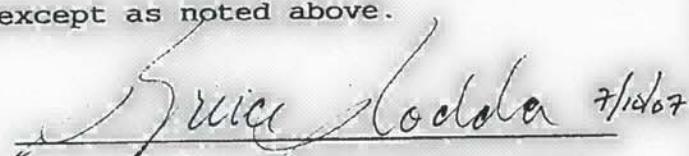
C

1 SIGNATURE AND CHANGES

2 RE: JOHN HANCOCK VS. ABBOTT LABORATORIES

PAGE	LINE	CHANGE	REASON
14,	18	Replace "loathe" with "loath" - typo	
131,	10	Delete lines 10 and 11 after the word tolerability and replace with "and adverse events." - clarification	
133,	13	Insert the word "and" after the word "groups." - clarity	
10			
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19			

20 I, BRUCE RODDA, Ph.D., have read the foregoing
21 deposition and hereby affix my signature that same is
22 true and correct, except as noted above.

23  7/14/07
24

25 BRUCE RODDA, Ph.D.

Rodda Deposition Exhibit 6

P's Exhibit ES



Marilyn J
Collicott/LAKE/PPRD/ABBO
TT
02/27/2001 10:12 AM

To stheriault@rsi-nc.com
cc
bcc
Subject today's meeting

Hi Sheila

Attached are the handouts for todays meeting at 3:00 CST.



agenda.pub



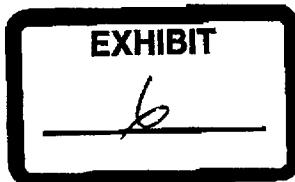
Investigator tracking.xls



R-Team scheduling.xls



Subject-CRF Tracking.xls



M99-114 INVESTIGATOR LIST

Investigator Last Name	Inv. #	State	Coordinator	Phone #	Total Screened	Total Randomized as of 1/30/08	Screen Failure Rate	Early Termination Rate	Completion Rate	Total Study Enrollment	CRFs In:	In-House as of 5/27/01
Backman	14272	WA	Christie Nease	(608) 282-0376	4	3						3
Baumel (A)	7379	FL	Alfonso Munoz	(305) 865-0063	26	15						12
Baumel (B)	7379	FL	Janeta Crislo	(561) 366-1123								5
Brion	7396	AR	Donna Langhoff	(501) 227-5061	16	7						13
Bromberg	15844	UT	Donna Baum	(801) 585-6051	28	14						9
DeBold	15066	MN	Diane Whipple	(952) 933-2739	17	12						1
Shankar	15842	FL	Suzanne Phillips	(727) 735-2191	7	6						6
Eitner	15880	FL	Maggie Szymczek	(954) 720-1899	17	16						5
Forda (T)	15842	NY	Michael Balotti	(516) 496-6506	3	2						1
Fred	12999	RI	Thomas Hock	(401) 467-7760	15	9						8
Gibson	15841	AR	Stuffy Parker	(601) 222-7406	26	18						18
Gilesen	15840	NB	Stephanie Cawley	(506) 722-7650	9	7						7
Haze	15839	MA	Patricia Sklar	(617) 734-7259	8	6						5
Hewitt	14345	GA	Ellen McKee	(404) 778-3176	12	9						7
Holmes	15856	NY	Mark Holmes	(716) 826-5126	11	5						5
Kaufman	14897	FL	Patricia Johnson	(305) 253-0206	18	7						7
Kopke	15062	OK	John Kopke	(918) 645-0366	21	15						15
Kory	15679	AZ	Stephen Kory	(602) 213-9273	20	10						10
Kung (H)	15855	FL	Monica Kung	(305) 253-1451	24	9						9
McGill (D)	15837	MO	Kathleen Anderson	(314) 362-1404	12	8						5
Rowbotham	14349	CA	George Rowbotham	(415) 825-7391	13	4						4
Shabani	18334	TX	George Maroulis	(713) 795-0033 x26	48	18						16
Simmons	15826	PA	Kathleen Hay	(717) 531-8894	7	6						5
Singer	16230	FL	Mercy Novero	(954) 433-5785	30	15						10
Sivakumar	15832	NC	Sowmya Nivash	(502) 822-2024	14	9						9
Stoddard	15923	NC	George Stoddard	(919) 752-4848	10	8						8
Storey	14349	NY	Paula Levin	(518) 438-0922 press	21	13						3
Sum	15897	CA	Robert Hayes	(604) 541-1561	4	3						3
Wink	15839	MA	Patricia Bailey	(716) 734-5926	10	6						6
Weinstein	15038	CA	Summer Young	(951) 933-7267	44	19						19
					505	269						234

Screen Failure Rate: 47%
 Early Termination Rate: 40%
 Completion Rate: 48%
 Total Study Enrollment: 84%
 CRFs In: 87%

[FILE]

[PAGE]

[DATE][TIME]

Screen Tracking

Page | PAGE

Highly Confidential

ABBT238331

M99-114 Early Terminations

Investigator	Subject #	Age	Days on Study Drug	Reason for Termination	Comments
Backonja	4467	37	1	AE	urea nitrogen level high panic at 56
Baumel	4145	85	1	AE	nausea, etc.
	4146	76	10	AE	dizziness, weakness, heart palpitations, headaches, blurred vision
	4147	85	11	AE	dizziness, weakness, sweating, blurred vision, heartburn, headache
	4228	73	unk	AE	hypoglycemic episode
	4231	73	27	AE	hallucinations
Biton	4260	82			
Bromberg	4113	69	10	AE	nausea, etc
	4115	45	5	AE	nausea, etc
	4117	50	7	AE	nausea, etc.
	4118	49	10	AE	dizziness, vomiting, nausea
	4125	85	1	AE	extreme nausea
DeBord	4051	71	9	AE	nausea, etc.
	4053	52	49	SAE	diabetic ketoacidosis
	4055	75	15	AE	int. nausea/vomit since 9/1, int abd bloating & constipation, decr. urine stream since 8/26
	4057	72	16	AE	intermittent nausea and vomiting
	4058		3	AE	dizziness, lethargy, vivid dreams, insomnia, increased neuropathic pain
	4060	57			
Drucker	4001	72	3.5	AE	joint pain in lower extremities
	4002	71	3	SAE	palpitations
	4003	78	0.5	AE	blurry vision
	4005	46			
	4008	72	1	AE	nightmares and intense neuropathic pain after 1st dose, whole body numb, wobbly, weak after 2nd dose
Eisner	4241	80	1	AE	nausea, etc. (went to ER)
Forda	4321	67	5	AE	disturbing dreams/anxiety
Fried	4083	66	14	SAE	syncope episode related to historical atrial fib (admitted to hospital 5/30)
	4087	74	4	AE	diarrhea, GI upset, fatigue, light-headedness (patient took every dose following a meal)
	4089	81	8	AE	dizziness
Gibson	4354	73	1.5	AE	nausea
	4359	31	27	AE	nausea and vomiting
	4367	32	12	AE	nausea and vomiting
Gleeson	4164	51	1	AE	dizziness, disorientation
	4165	51			
	4167	70			
Haag	4337	43	5.5	AE	dizziness ~2hrs post-dose x 10 episodes
	4340	72	5	AE	difficulty falling asleep, awakening more frequently
	4341	85	36	AE	mental status changes
Hewitt	4311	52	8	AE	nausea and vomiting
Holmlund	4193	53	7	AE/SAE	vomiting, fatigue/broken pelvis
	4195	60	7	AE	nausea, vomiting
	4197	82	4	SAE	chest pain
Kafka	4417	74	6	AE	nausea, vomiting
	CMW		7	AE	jaw pain, insomnia, increased BP, heart palpitations, tingling
	4419	61	46	AE	nausea and vomiting
Kipnes	4065	64	3.5	AE	nausea
	4066	35	25	AE	nausea
	4070	45	10	SAE	left arm pain
	4072	70	7	AE	nausea, etc.
	4075	74	2	AE	severe nausea, shakiness
Kirby	4178	62	9	AE	backache
	4501	55	9	AE	unsteady gait, nausea, indigestion
Kluge	4131	70	8.5	AE	nausea, etc
	4133	66	5.5	SAE	high blood glucose and chest pain due to GI problems (hospitalized 6/6-6/10)
McGill	4387	66	7	AE	nightmares, insomnia, nausea
	4390	59			
Shabani	4450	56	30	AE	stomach ache
	4451	60	18	SAE	chest pain, shoulder pain
	4455	66	1	AE	got sick after first day
	4456	57	7	AE	headaches, lightheadedness, depression, rectal bleeding, sleeplessness caused by stomach acid

M99-114 Early Terminations

	4462	55	10	AE	vomiting, stomach sickness, diarrhea, fluttering, moaning, crying, shaking, confusion
	4483	68	6	AE	depressing dreams, LOE
	4493	61	13	AE	nausea, diarrhea, vomiting, headache
Simmons	4273	58	11	AE	GI sx, cognitive dysfunction, unusual dreams, bad taste in mouth, headache, bodyache
	4275	69	10	AE	vomiting, nausea, headache, vivid dreams, diarrhea, chills
	4276	56	19	AE	nausea
	4277	56	9	AE	nausea, vivid dreams
Singer	4401	53		AE	angina/secondary to coronary artery blockage
	4402	67	12	AE	dizziness, vomiting
	4403	57	25	AE	worsening insomnia
	4408	68	8	AE	vomiting
Sivakumar	4036	59	3.5	AE	nausea, etc.
	4040	57	7	AE	apprehensive, irritable, tinnitus, headache, burning eyes, diarrhea, vivid dreams
	4041	51	1	AE	nausea, vomiting, diarrhea
Steel	4209	68	22	AE	light-headed, dizzy
	4210	73	9	AE	vomiting
	4215	60	10	AE	severe nausea
	4216	52			
Storey	4098	70	6.5	AE	nausea, etc.
	4100	56	3	AE	nightmares
	4102	69			
Weinstein	4020	73			
	4021	65	13	AE	coughing, sore throat, cold sx (went to ER)
	4024	63			
	4488	79	6	AE	dizziness, nausea, diarrhea

Rodda Deposition Exhibit 2

D's Exhibit BR

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Summary of Anticipated Expert Testimony

by

Dr. Bruce E. Rodda

The following is a summary of the anticipated expert testimony of Dr. Bruce E. Rodda in connection with the action entitled John Hancock Life Insurance Company, John Hancock Variable Life Insurance Company, and Manulife Insurance Company (f/k/a Investors Partner Insurance Company) v. Abbott Laboratories, U.S.D.C. (Mass.) Civil Action No. 05-11150-DPW. Dr. Rodda has been asked by Munger, Tolles & Olson LLP, on behalf of Abbott Laboratories, to provide the Court with expert testimony regarding the development of new pharmaceutical compounds, including without limitation, the statistical aspects of evaluating and interpreting the results of clinical trials in support of these developmental activities. Dr. Rodda's testimony may include, inter alia, expert testimony regarding the Abbott study referred to as ABT-Protocol M99-114, A Randomized, Double-Blind Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Polyneuropathy.

26 Feb 07



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A summary of Dr. Rodda's training and experience can be found at pages 1-3 of the Summary of Anticipated Expert Testimony by Dr. Bruce E. Rodda served on plaintiffs on January 19, 2007.

This summary of Dr. Rodda's anticipated testimony is expected to include opinions regarding the anticipated testimony of Dr. Barry Gold with regard to statistical issues, the anticipated testimony of Dr. William Fairweather, the clinical protocol and clinical study report for Abbott study ABT-M99-114, and various statistical topics associated with clinical development generally and study ABT-M99-114 in particular.

Dr. Rodda will testify based upon his own experience, using information and materials available in the public domain (including, but not limited to, information from the United States Food and Drug Administration's ("FDA") website and the European Medicines Agency ("EMEA") website), and upon testimony and materials obtained in discovery in this action. During his testimony, Dr. Rodda may make reference to specific evidence contained in documents or witness testimony.

The opinions and analysis contained in this summary of Dr. Rodda's anticipated testimony are based on currently available information. Dr. Rodda's work is continuing and he plans to analyze any new information. Dr. Rodda may modify this summary in light of such new information. The present summary of Dr.

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Rodda's anticipated testimony may be supplemented by his deposition testimony.

Dr. Rodda is expected to opine on Dr. Gold's and Dr. Fairweather's anticipated testimony regarding the statistical considerations for Protocol M99-114 and the outcome of that study. He may opine on areas in which he feels either Dr. Gold's anticipated testimony or Dr. Fairweather's anticipated testimony is incorrect, incomplete, or unclear. Some of the comments that Dr. Rodda is expected to make in this regard are as follows.

Dr. Rodda's anticipated testimony may be grouped into three related areas – general considerations, power and sample size considerations, and results and conclusions regarding Study M99-114.

GENERAL – Dr. Rodda may opine that the underlying approach to designing and evaluating a comparative clinical trial is to assume, at the outset, that the treatments under investigation do not differ in their response. This is referred to in statistical terminology as the “null hypothesis”. The study is then conducted with the objective of collecting information that will refute this hypothesis if the experimental treatment is, in fact, superior to the control treatment. If a substantial difference favoring the experimental treatment is observed when the study is completed, the conclusion would be that the experimental treatment is superior to the control. On the other hand, if a small difference was observed

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that was not inconsistent with the null hypothesis of no difference between the treatments under study, the conclusion would be that any real difference between the experimental and control treatments was too small to be of clinical importance. In the context of Abbott study M99-114, this means that Abbott planned Study M99-114 with the expectation that ABT-594 was superior (and not equal) to placebo. Abbott designed Study M99-114 to have a high likelihood of producing results that would support the conclusion that ABT-594 was superior to placebo if, in fact, ABT-594 was truly superior. The results of M99-114 provided a substantial difference between each of the three doses of ABT-594 and placebo with respect to the primary variable (Likert pain scale), clearly confirming the superiority of each of the three doses of ABT-594 compared with placebo.

The results of a clinical trial are analyzed by statisticians to provide a basis for reaching conclusions. In his anticipated testimony (p. 15, line 16) Dr. Gold states that after data are "sorted into groups by dose and drug, one or more statistical tests will be applied." Dr. Rodda is expected to provide expert opinion that when the study is completed and the data have been unblinded, the statistical team will perform a complete statistical evaluation of the study results based on a statistical analysis plan (SAP) that was designed prior to unblinding the clinical data. This plan for the statistical analysis will sometimes be included in the body of the protocol or may be written as a standalone document for complex studies. If a standalone SAP is written, it is often appended to the protocol. The statistical

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analysis will be performed in concert with clinical experts and will be far more extensive than "one or more statistical tests".

With regard to Dr. Gold's anticipated testimony (page 5, line 4) Dr. Rodda may opine that Dr. Gold's use of the term "statistically evaluate" is unclear. Dr. Rodda is expected to discuss that while statistical concepts and techniques are important for the evaluation of safety and efficacy, there are other essential sources of input, e.g., clinical knowledge and experience that are essential in the evaluation of clinical trials.

POWER AND SAMPLE SIZE – Every clinical trial is different and the outcome of each clinical trial is unpredictable. If the identical trial were conducted many times, the results would differ each time for a variety of reasons. In addition to the uncertainty caused by random variation, other factors affect the confidence we have in the inferences made at the conclusion of a study. Some of these factors are the variability of the basic measurement, the size of the true difference between the experimental treatment and control (which is unknown and must be estimated from the study), the probability with which one wishes to detect a true difference if it exists (power), the risk one is prepared to take in declaring a true difference exists when it does not (Type I, or alpha, error), and the number of patients participating in the study.

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For example, to estimate the sample size for Protocol M99-114, Abbott used information from Protocol M98-833. That study suggested that a meaningful difference would be 11.4 units on a 100 point Likert scale with an associated standard deviation of 24.4 units, yielding a standardized difference (or treatment effect) of 0.46. Abbott utilized this standardized effect size, a power (or probability of getting a statistically significant outcome if the anticipated difference was real) of at least 0.8, and an acceptance of a 5% risk of falsely declaring ABT-594 superior to placebo, resulting in a planned sample size of approximately 80 patients in each group.

Dr. Rodda is also expected to testify that power is a concept that is only relevant for planning a clinical trial and is of little value in the interpretation of the results of a study.

Organizations sponsor clinical trials because they believe that their experimental treatment will have a clinically important difference over the standard treatment or a negative control. When a sponsor commits to performing a clinical trial, the sponsor wants to minimize the likelihood that the study will be inconclusive. Said differently, if the new treatment has a clinically important effect of Δ , the sponsor wants the study to have a high likelihood (or power) of demonstrating that effect with a "statistically significant" result. That is, the sponsor does not want the study to result in a conclusion of "ineffective" or "inconclusive" if the product really is superior to the control. Intuitively, because a larger trial provides more

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information than a similar smaller trial, a larger trial will be more likely to be conclusive than a smaller trial. Because clinical trials are very expensive, it is critical that studies be designed with the proper number of patients to satisfy their goals. Too many patients will result in unnecessary exposure of patients to experimental treatments and will be unnecessarily expensive. Too few patients, on the other hand, may result in an inconclusive study with the potential need to repeat it. For these reasons, a clear strategy must be followed for determining the number of patients required in a clinical trial.

Four basic factors influence the size of a clinical trial.

Variability – If an effect is associated with very small variability (i.e. the effect is very consistent), few subjects would need to be evaluated in a clinical trial to have confidence regarding any decisions made about the particular effect of interest. In contrast, if the effect is quite variable or inconsistent, conclusions based on the information provided by the same few patients would be less convincing. To provide the additional information necessary for similar confidence in the two cases, more patients must be evaluated when there is greater variability. For any scientific measure, precision increases and the likelihood of error decreases with additional information. In the clinical trial context, this information corresponds to a decrease in variability and/or an increase in the sample size.

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Clinically Important Difference between the Experimental and Control Treatment

- The second factor that influences the size of a study is the difference between the experimental treatment and the control that is clinically important. If the true (but unknown) difference between the comparative agents is very small, the study will require a large number of patients to provide adequate evidence to conclude that the specified difference is not zero as stated in the null hypothesis, but that a real difference exists between the treatments. On the other hand, if the sponsor believes that its new product is superior to the standard by a substantial margin, fewer patients will be required to obtain a statistically significant result if the true difference between the two treatments is large.

Risk of a False Positive Conclusion - The third consideration influencing the size of a clinical trial is the probability of falsely concluding the new treatment is superior when it is not. Consider that even if the experimental treatment and control treatment had inherently identical effects, the results of any specific study could randomly favor the experimental treatment to a degree that the (incorrect) conclusion would be that the experimental treatment is superior to the control treatment. This probability is also called a Type I error or alpha error (also referred to as the level of statistical significance) and is chosen before the study begins. At the conclusion of the study, the null hypothesis is tested against this alpha error standard (e.g. $p<0.05$), and if the results of the study are more extreme than would be expected if there were no true therapeutic difference, the result would be called "statistically significant (at the $p<0.05$ level)" and the

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conclusion would be that the experimental treatment is effective. The probability of making this conclusion in error would be 0.05 (or 1/20) in this example.

The Type I error is usually set at 0.05 (or 5%) and this is a standard recommended by the FDA and other regulatory agencies. Hypothesis tests routinely use this cutoff as the definition of "statistical significance". In the present study, the alpha level was chosen to be 0.05 and was specified in the protocol. At the conclusion of Study M99-114, the results of comparing each dose of ABT-594 with placebo were "statistically significant" ($p < 0.05$), implying that each dose is truly superior to placebo with respect to pain.

Risk of a False Negative Conclusion/Power – It is also possible to incorrectly conclude that a clinically important effect is absent. Suppose that the experimental treatment is truly superior to the control treatment by, say Δ units. The results of any study are unpredictable, and even though the experimental treatment is, in fact, superior to the control treatment, the outcome of a particular study might result in a difference that was quite small, just by chance. In that case, the test of the null hypothesis would not be rejected (that is p would be greater than 0.05), and the incorrect conclusion would be that the experimental treatment is not superior to the control treatment. This type of error is referred to as Type II error or Beta error. The probability of correctly concluding that the experimental treatment is superior to the control is one minus the probability of incorrectly concluding the treatment is effective. The probability of correctly

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concluding the experimental treatment is superior is termed "power". Sponsors and investigators usually want this probability to be quite high and often select sample sizes that will provide 80% power. In study M99-114, the planned power was 80% power.

The relationships among the various factors contributing to the estimation of the sample size may be clearer by considering the following equation:

$$n = \frac{2(z_{\alpha/2} + z_{\beta})^2 \sigma^2}{\Delta^2}$$

where: n is the sample size in each treatment group and

$z_{\alpha/2}$ is an index of the risk of a false positive –
the higher $z_{\alpha/2}$, the lower the risk (1.96 in Study M99-114)

z_{β} is an index of the risk of a false negative –
the higher z_{β} , the lower the risk (0.84 in Study M99-114)

σ is the standard deviation – the measure of variability ($\sigma = 24.4$ from Study M98-833)

Δ is the difference the study is designed to detect ($\Delta=11.4$ from Study M98-833) (Note that $\Delta/\sigma = 0.46$ is the
standardized treatment effect Study M99-114 was designed
to detect).

Note that the z-values above are values of standard normal deviates and are indexes of the probabilities; they do not represent the actual probabilities.

Dr. Rodda is expected to opine that the sample size for the Protocol M99-114 was estimated using a standard statistical approach for the comparison of two means. While there are usually several choices that may be appropriate for

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estimating the sample size in any clinical trial, the procedures used in this study were consistent with good statistical practice and the sample size was appropriate for detecting the pre-specified standardized treatment effect of 0.46 in the primary variable with 80% power at an alpha level of 0.05.

It should be understood that just because a sample size has been chosen which appears to provide 80% power, it does not imply that there is an 80% chance that a given trial will be successful. Power is a concept that is only relevant for planning a clinical trial and is of little value in the interpretation of the results of a study.

Even if the planning has been appropriate and the calculations are correct consider the following points.

1. The assumptions used to estimate the sample size are approximations.

The estimate of variability used in the calculation of sample size is derived from previous experience, often in a different environment than the given study. The variability that will actually occur in the planned study may be greater or less than used in the power calculations. In this case situation, the power would be lower or higher than anticipated.

2. The true difference between the treatments is unknown and the study may result in a higher or lower difference than that used to estimate the sample size.

3. The new treatment may not actually be superior. (In fact, if a study correctly results in this conclusion, the study has not been a failure. The study has reached the correct conclusion, even though it was not the conclusion that was desired.)
4. Even if the new treatment is superior, the difference actually seen in a particular study may not be conclusive, just by chance.

Dr. Rodda will be prepared to discuss the concept of power as it relates to estimation of sample size and how this is a quantifiable risk chosen at the discretion of the sponsor. He will also be prepared to discuss the fact that neither "power", nor "statistical significance" is associated with the validity of a study. The validity of a study is dependent on its design and implementation. Two studies of the same design but of different sizes will both be equally valid if they are properly designed and executed. The larger study will provide more information and precision regarding the conclusions than the smaller study, but they can be equally valid.

In Dr. Gold's anticipated testimony (page 8, line 1 and preceding), he states that variability is an important factor in the determination of the size of a study. Dr. Rodda is expected to opine that sample size is not determined solely by making certain assumptions about variability in the data. Sample size is also dependent

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on three other considerations as described previously: the risk (probability) of declaring an ineffective treatment to be effective at the conclusion of a study, the risk of not detecting a true clinically important difference at the conclusion of the study (and thereby erroneously concluding that an effective treatment is ineffective), and the magnitude of the clinically important treatment effect the study is designed to detect.

While Dr. Gold's contention (page 8, line 3) that the statistician's duties typically include estimating "very closely" how many patients must be enrolled, the term "very closely" is not correct. Dr. Rodda is expected to opine that estimating sample size is dependent on both the clinically important difference and the estimated variability of response, in addition to the considerations regarding false positive and false negative errors presented previously. The variability used in estimating a sample size is often an estimate from other studies and the estimated sample size is only as good as the estimate of the variability used to calculate it.

Beginning on page 8, line 5 of his anticipated testimony, Dr. Gold states that the "power of a study refers to the statistical test they have chosen and the probability that the test will fail to detect a true difference between two groups." Dr. Rodda is expected to opine that the "power" of the study is not only a function of the test to be used in the analysis of the primary variable, but more importantly, refers directly to the probability that the study, as designed, will find

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the pre-specified clinically important difference to be statistically significant at a pre-specified risk of a false positive outcome (declaring an ineffective drug to be effective). It is not, as Dr. Gold states, the probability of failing to detect a true, pre-specified, difference; it is the probability of actually detecting that difference. In addition, it is not the statistician who wishes to detect the difference; it is the sponsor, through the project team (and often following discussions with the FDA), who defines the pre-specified difference and is most interested in the outcome.

RESULTS AND CONCLUSIONS OF THE M99-114 STUDY– Dr. Rodda is also expected to testify that both the International Conference on Harmonization (ICH) and the U.S. Food and Drug Administration (FDA) recommend using as complete a dataset as possible for evaluating both safety and efficacy. Any patient that can be evaluated for efficacy should be included in the primary analysis. The analytic approach proposed for protocol for study M99-114 is consistent with the intent of this guidance. In fact, the protocol states that “all subjects receiving at least one dose of study drug with at least one diary-based baseline and at least one post-baseline pain assessment for the diary-based Pain Rating Scale will be included in the intent-to-treat analysis.” The description of this dataset is included in the protocol and was defined before the study was begun. This dataset is consistent with ICH E-9 (Statistical Principles for Clinical Trials) which describes such a dataset as being “as complete as possible and as close as possible to the intention-to-treat ideal of including all randomized subjects.” The clinical study report for Protocol M99-114 includes 225 of the 266 patients

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randomized to treatment in the primary efficacy analysis; all 266 patients are included in the safety analysis.

Patients withdraw from clinical trials for many reasons. Some are random and do not influence or bias the conclusions. However, patients may withdraw from clinical trials for two primary reasons that may be related to the treatment they receive - the adverse events they experience are such that they no longer wish to participate in the study or the treatment they are receiving is insufficiently effective to support their continued participation in the study. In either case, patients who withdraw from a study provide valuable information regarding the safety and efficacy of the product under investigation. Excluding patients from the analysis of clinical trials can substantially bias the conclusions reached. It is for this reason that both ICH guidelines and the FDA recommend using all patients with valuable data in the analysis of safety and efficacy. In reviewing the documentation of Abbott's deliberations prior to terminating enrollment, there was never a reference to using less than all evaluable patients in the appropriate analyses. Dr. Rodda may opine that given the above, Dr. Fairweather's position of considering only 137 patients for evaluation is scientifically inappropriate and inconsistent with ICH and FDA standards. To use only the 137 completing patients as Dr. Fairweather suggests would not be consistent with good scientific practice, would bias the results in favor of ABT-594, and would not be acceptable to the regulatory and scientific community.

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Documents relating to internal meetings at Abbott suggest that Abbott became aware at some point that they would not meet the enrollment goals in the planned enrollment period for Study M99-114. During the period preceding Abbott's decision to terminate enrollment, several activities took place in an effort to determine the impact of these factors on the probability that the study would satisfy its goal of distinguishing ABT-594 from placebo. In addition to efforts targeted at improving enrollment, Abbott evaluated the effect of smaller sample sizes on the probability (power) of detecting their predefined standardized treatment effect of 0.46. This was done in a fully blinded manner and assumed that all patients would be evaluable for efficacy. This activity focused on the following question: if the study concludes with a reduced number of patients, what is the probability (power) of detecting (finding statistically significant, $p<0.05$) the proposed treatment effect of 0.46 between ABT-594 and Placebo? An example of the power considerations of this evaluation is contained in a memo from Mr. James Thomas to Ms. Rebecca L. Brown on 9/28/2000 in preparation for a meeting on the topic. This table is reproduced in part below.

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<u>Option</u>	<u>Sample Size</u>	<u>Effect</u>	<u>Power</u>
1	20	.46	0.29
2	25	.46	0.36
3	30	.46	0.42
4	35	.46	0.48
5	40	.46	0.53
6	45	.46	0.59
7	50	.46	0.62
8	55	.46	0.67
9	60	.46	0.71
10	65	.46	0.74
11	70	.46	0.77
12	75	.46	0.80
13	80	.46	0.82

Entries in this table include possible sample sizes (per group), the hypothesized treatment effect Study M99-114 was designed to detect and the power to detect this difference for each sample size. It can be seen from this table that the actual number of patients at the termination of enrollment (266 or about 65 per group) would provide 74% power to detect the hypothesized 0.46 treatment effect (compared with an initial power of at least 80% as cited in the protocol). This activity provided Abbott with a full understanding of the probabilities of Abbott's detecting their chosen effect for several smaller sample sizes. However, if the true treatment effect was larger than 0.46, the probability of finding this larger difference with the reduced sample size would increase.

It is common in clinical trials for actual enrollment to be less than planned. The only risk of stopping enrollment in a study with fewer patients than planned (as it relates to power) is that the treatment difference between the experimental agent and the control agent may not be statistically significant. In these cases, the

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sponsor may accept that the study's power to detect the originally hypothesized difference may be lower than used in estimating the study's size. There are several strategic considerations that may affect the sponsor's decision. Extending a study for an additional year, for example, to acquire the planned sample size may increase the cost to an unacceptable degree or expose the product to a new competitive agent such that the higher risk of extending the study may be unacceptable to the sponsor. In addition, after the study has begun, factors such as safety considerations with the new treatment or the introduction of a new competitor may require that a successful product possess a larger superiority over the control treatment than was originally planned. In this case, a reduced sample size may be consistent with a comparable, or perhaps greater, power than originally planned, since larger effects require smaller sample sizes.

Dr. Fairweather opined that of the 266 patients enrolled in this study, only 137 were "usable". This suggests that the remaining patients provided no information regarding the safety and efficacy of ABT-594. As stated earlier in this summary, those patients who withdraw from a clinical trial provide important information regarding the safety and efficacy of the products under study. ICH guidelines and the FDA would demand that all relevant information be used in the analysis; patients who withdraw cannot be considered "unusable" for either safety or efficacy. In addition, if one were to accept Dr. Fairweather's contention regarding usability, the original sample size of 320 patients would need to be increased by

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a factor of 266/137 (1.94), to a total enrollment of 621 patients to net 320 "usable" patients.

Dr. Rodda may opine that although Abbott terminated enrollment before reaching the target of 320 patients, Abbott carefully evaluated the possible outcomes of the study based on the reduced sample size and concluded that the reduced power associated with the originally hypothesized treatment effect was acceptable. Referring to the table above, Abbott knew that its power to detect their original hypothesized treatment effect of 0.46 would be approximately 74%, rather than the planned 80%. Viewed somewhat differently, while the initial plan had an 80% power to detect a treatment effect of 0.46, the actual intent-to-treat sample of 225 patients (Clinical Study Report, Table 11.4a) had an 80% power to detect a treatment effect of 0.56. Since the actual differences observed between the active treatment groups and the placebo group were all in the range of 0.8 to 0.9 units on the 11 point Likert scale (and were all statistically significant at the p<0.05 level), the study clearly had adequate power to address the primary objective of the study, and the study should be considered conclusive (successful) in this respect.

Although Abbott did not know the margin by which ABT-594 would be superior to the control when Abbott decided to terminate enrollment in this study, that margin was substantially larger than originally anticipated. This difference was manifested in results that were statistically significant, rendering the question of

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adequate power (i.e. the probability of obtaining a statistically significant result) moot. Although both Dr. Gold and Dr. Fairweather had comments regarding the effective sample size of study M99-114, neither questioned that the study was conclusive in demonstrating that ABT-594 was superior to placebo with respect to the primary efficacy variable, despite a sample size that was somewhat less than originally planned.

References

1. European Medicines Agency: Scientific Guidelines for Human Medicinal Products: ICH E6 – Guideline for Good Clinical Practices. 1996.
2. European Medicines Agency: Scientific Guidelines for Human Medicinal Products: ICH E9 – Statistical Principles in Clinical Trials. 1998.
3. The World Medical Association: World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. 2004
4. 21 CFR 312.40 General requirements for use of an investigational new drug in a clinical investigation
5. Abbott communiqué Dr. James Thomas to Ms. Rebecca L. Brown – 9/28/2000
6. Summary of proposed expert testimony by Dr. Barry I. Gold
7. Summary of proposed expert testimony by Dr. William R. Fairweather

Documents Reviewed by Dr. Bruce Rodda

<u>Bates Nos.</u>	<u>Date</u>	<u>Description</u>
-----	10/13/06	Expert report of Barry I. Gold
-----	01/19/07	Expert report of Dr. William R. Fairweather
-----	6/23/06	Supplemental Complaint
-----	2/6/06	Hancock's Objections & Responses to Abbott's First Set of Interrogatories
-----	9/27/06	Marilyn Collicott deposition transcript
ABBT 0004410-0004415	4/00/00	Collicott Exhibit 6
ABBT 0004436	8/00/00	Collicott Exhibit 10
ABBT 0004443-0004447	9/00/00	Collicott Exhibit 12
ABBT 0004448-0004454	10/00/00	Collicott Exhibit 15
ABBT 237155-237159	10/9/00	Collicott Exhibit 16
ABBT 0004455-0004459	11/00/00	Collicott Exhibit 17
ABBT 0004460-0004464	12/00/00	Collicott Exhibit 22
ABBT 0000322-0000327	1/00/01	Collicott Exhibit 27
ABBT 240624	1/8/01	Collicott Exhibit 28
ABBT 242693-242699	1/16/01	Collicott Exhibit 29
ABBT 0001748-0001758	4/23/01	Collicott Exhibit 39
ABBT 335154	5/4/01	Collicott Exhibit 41
ABBT 239029	5/18/01	Collicott Exhibit 42
ABBT 240374-240412	10/15/02	Collicott Exhibit 49
-----	9/29/06	Bruce McCarthy deposition transcript and all exhibits
ABBT 0020894-967	10/99/99	Draft 10/7/99 M99-114 Protocol
ABBT 0065818-0078893	-----	CD containing: Clinical Study Report and Clinical Protocol
-----	-----	CD containing: Amendment for Study M99-114
ABBT 159274	9/3/99	Email to Waleska from Siber
ABBT 51889	12/21/99	Email to Siebert from Thomas
ABBT 65818-65896	2/8/00	Protocol M99-114
ABBT 242154	5/25/00	Letter to Hoffstetter from Collicott
ABBT 33462-33467	5/31/00	Site breakdown/enrollment for M99-114
ABBT 79825-79826	6/20/00	Emails between Nunn and Thomas
ABBT 241296-241297	6/27/00	Emails among McCoy, Rowbotham and Collicott re barrier to enrollment
ABBT 161395	7/6/00	Email to Matalonis, et al from Garavalia
ABBT 82516	7/7/00	Email to Morris, et al from McCarthy
ABBT 239985-239988	7/10/00	Site breakdown/enrollment for M99-114
ABBT 83022	7/13/00	Email to Landsberg, et al from Collicott
ABBT 161644-161645	7/25/00	Emails among Barnesen and Powers
ABBT 78935-78941	8/7/00	Email to Thomas from Hansen with patient listing
ABBT 335227-335307	8/23/00	ABT-594 Development Plan
ABBT 80232-80237	8/29/00	Email to Kacos from Thomas with data for power curves
ABBT 241302	8/31/00	Letter prototype to investigators from Collicott
ABBT 51907-51908	9/28/00	Power calculations

ABBT 82259	9/28/00	Email to Brown from Thomas with power calculations
ABBT 51892-51905	9/28/00	Email to Brown from Thomas with power calculations
ABBT 233741-233749	9/28/00	CT Recruitment and Centralized Screening Program
ABBT 237155-237159	10/9/00	Email to Nunn from Collicott with investigator tracking list
ABBT 107607-107609	10/30/00	Email to Biarnesen from Silber with list of project review questions
ABBT 109399-109400	11/22/00	Email to Morris from McCarthy with items for meeting discussion
ABBT 241843-241847	11/28/00	Email to Schanzenbach from Collicott
ABBT 81606	11/29/00	Email to Kacos from Thomas with confidence intervals for difference
ABBT 242373	12/6/00	Email to Biarnesen from Collicott re randomization goals
ABBT 233539-233540	12/14/00	Email to Schanzenbach from Collicott "decided to end enrollment as of 1/5/01"
ABBT 240624	1/8/01	Email to Schanzenbach from Collicott
ABBT 81459-81460	1/12/01	Email to McCarthy from Thomas with adverse event experience
ABBT 233000	1/15/01	Email to Schanzenbach from Collicott
ABBT 242693-242699	1/16/01	Meeting agenda with tables of investigators and early terminations
ABBT 8169-8176	Feb 2001	Descriptive memo on marketing prospects
ABBT 246076-246084	Feb 2001	Descriptive memo on marketing prospects
ABBT 242650	2/5/01	Tracking report
ABBT 242503	2/12/01	Tracking report
ABBT 242681-242688	2/13/01	Meeting agenda with tables of investigators and early terminations
ABBT 237944	2/20/01	Tracking report
ABBT 233001	2/26/01	Email from Brownell to Collicott re tracking report
ABBT 238329-238335	2/27/01	Meeting handouts with tables of investigators and early terminations
ABBT 298380-298385	3/5/01	Meeting minutes: Pain Strategy Decision Analysis
ABBT 297530-297555	3/7/01	Abbott Portfolio Review
ABBT 238328	3/13/01	Tracking report
JH 8074-8211	3/13/01	Research Funding Agreement by Hancock and Abbott
ABBT 240978	3/20/01	Tracking report
ABBT 79111-79119	5/23/01	Adverse event experience tables
ABBT 241331-241560	7/31/01	M99-114 Analysis
ABBT 241298-241300	8/14/01	Study enrollment graphs
ABBT 80451	2/19/02	Email to Olson from Thomas "screening failure rate 47%"
ABBT 79395	3/6/02	Email to Biarnesen from Thomas indicating blind broken 4/23/01
ABBT 51885-51888	-----	Power curves
ABBT 155581-155587	-----	Initial Portfolio Prioritization

JH8153 - JH8210	February 2001	Descriptive Memoranda
ABBT0104016-0104017	11/21/00	Email from McCarthy to Silber
ABBT01214045- 1214046	12/18/00	Email from Biarnesen to Robinson
ABBT0122646-0122718	11/17/00	ABT-594 Project Review